Objective: To review our institutional experience of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) and N2-N3 neck disease with respect to neck recurrence after chemoradiation without planned neck dissection (ND).

Design: Retrospective study.

Setting: Tom Baker Cancer Centre, Calgary, Alberta, Canada.

Patients: Fifty-four adults with locally advanced SCCHN and N2-N3 neck disease.

Interventions: Eighty consecutive patients were treated with chemoradiation, 70 Gy given as 2 Gy daily for 7 weeks, with cisplatin, 20 mg/m², given on the first 4 days of weeks 1 and 5. Of the 80 patients, 54 were evaluable.

Main Outcome Measures: Primary outcomes were overall survival and absence or presence of neck disease after chemoradiation. Secondary outcomes included disease-specific survival and locoregional recurrence-free survival.

Results: Median follow-up of living patients was 35 months. Patients with a complete response (CR) did not have any planned ND. Factors associated with the absence of recurrent neck disease included CR (\( P < .001 \)), younger age (\( P = .02 \)), and better Karnofsky Performance Status (\( P = .049 \)). In patients achieving CR, 2-year overall, disease-specific, and locoregional recurrence-free survival was 92%, 95%, and 95%, respectively. Three of the 43 patients (7%) with N2 lesions obtaining CR subsequently experienced a neck recurrence at a median of 15 months (range, 7-24 months).

Conclusions: In these patients with locally advanced SCCHN and N2-N3 neck disease treated with chemoradiation and achieving CR, only a few patients with N2 neck disease experienced recurrence despite the absence of planned ND. Prospective trials are needed to identify patients with N2 neck disease who may still benefit from planned ND after chemoradiation. There were not enough patients with N3 neck disease to make any recommendations.

had an initial CR, 3 (7%) experienced a delayed neck recurrence after treatment (ie, there was no planned ND). Follow-up assessments were performed every 1 to 2 months for the first year, every 2 to 3 months for the second year, every 4 to 6 months for the third year, and every 6 months thereafter.

**STUDY END POINTS AND STATISTICS**

The primary end points included overall survival and the presence or absence of neck recurrence. The secondary end points included disease-specific survival and locoregional recurrence-free survival. All the events were measured from the date of first treatment to the date of the recurrence or the date of the last follow-up visit. Survival rates were estimated using Kaplan-Meier statistical methods. All the statistical analyses were performed using a software program (SPSS version 13.0 for Windows; SPSS Inc, Chicago, Illinois). For comparison of medians and means, the binary backward logistic regression statistic was used.

**INITIAL RESPONSE TO CHEMORADIATION**

The CR rate (no evident disease at the primary site or nodal regions) as noted by findings from physical examination, imaging, or both was 85% (46/54). Posttreatment imaging was performed in 17 patients (31%). Thirteen patients underwent CT, and 3 underwent PET and showed no residual disease. Computed tomography picked up 1 ICR. The remaining patients were deemed to have had a CR by findings from clinical examinations on subsequent follow-up visits. Of the 46 patients who had an initial CR, 3 (7%) experienced a delayed neck recurrence at a median of 15 months (range, 7-24 months) after treatment. Patients obtaining a CR as determined by findings from physical examination, imaging, or both received no further treatment (ie, there was no planned ND). Follow-up assessments were performed every 1 to 2 months for the first year, every 2 to 3 months for the second year, every 4 to 6 months for the third year, and every 6 months thereafter.

**RESULTS**

Response evaluation included physical examination, imaging, or both 4 to 6 weeks after treatment. Patients were classified as having either a complete response (CR) or an incomplete response (ICR). Posttreatment CT, magnetic resonance imaging, and positron emission tomography (PET) were performed at the discretion of the treating oncologist. Salvage surgery of the primary site or neck was offered to patients with suspected residual disease after treatment. Patients obtaining a CR as determined by findings from physical examination, imaging, or both received no further treatment (ie, there was no planned ND). Follow-up assessments were performed every 1 to 2 months for the first year, every 2 to 3 months for the second year, every 4 to 6 months for the third year, and every 6 months thereafter.

**Figure 1.** Summary of patient outcomes according to whether the patient had a complete response (CR) or an incomplete response (ICR). N category is according to the American Joint Committee on Cancer 1997 staging criteria.
examination of the primary site and neck area. Two of the 3 patients had recurrences in the neck area, and 1 had a recurrence in the primary site and the neck area. Only 1 patient proceeded to salvage neck surgery. This patient underwent a right modified radical ND and selective left ND. Pathologic examination of the right side of the neck showed extranodal disease, and the involved neck underwent repeated irradiation. Results for the left side of the neck were negative. This patient died of aspiration pneumonia 7 months after the repeated surgery. The second patient was initially lost to follow-up and returned at 10 months with an inoperable neck recurrence. The third patient had inoperable recurrences in the primary and neck areas. In summary, the negative predictive value (NPV) of a CR was 93% (true negative divided by the sum of true negative and false negative). This finding is consistent with a recent publication from the Cleveland Clinic that showed an NPV of 93% by physical examination alone.10

An ICR to chemoradiation was noted in 15% of patients (8/54). Five of these 8 patients had an ICR of the primary site. Three patients with suspected positive neck nodes on initial follow-up physical examination with or without CT underwent selective unilateral ND and diagnostic imaging 2 to 4 months after chemoradiation. All 3 patients had pathologically negative specimens. Therefore, not all incomplete responders will have residual cancer in the neck. These 3 patients remain alive and without locoregional disease, but 1 has developed lung metastases. The remaining 5 patients with ICR did not undergo salvage surgery for the following reasons: ICR of the primary site and neck resulting in inoperability (n = 3), concurrent distant metastases (n = 1), and medically unfit for operation (n = 1). All 5 patients subsequently died of their disease at a median of 10 months.

OVERALL AND DISEASE-SPECIFIC SURVIVAL

Median follow-up for living patients was 35 months (range, 8-58 months). Kaplan-Meier actuarial 2-year overall survival for the entire cohort was 82% (Figure 2).

Those who had an initial CR to therapy had better 2-year overall survival than their counterparts who did not (92% vs 25%; P < .001) (Figure 3). Similarly, 2-year disease-specific survival was higher in patients with CR compared with those with ICR (95% vs 33%; P < .001) (data not shown). Those who did not have an ND had similar 2-year survival compared with those proceeding to ND (82% vs 75%; P = .28).

ANALYSIS OF RECURRENT NECK DISEASE

Of the patients analyzed, 46 (85%) had no recurrent neck disease, whereas the remaining 8 patients (15%) had residual or recurrent neck disease. Several factors were analyzed retrospectively in this study to assess their association with the absence or presence of neck recurrence. Complete response, age, and initial Karnofsky Performance Status score showed significant associations in predicting residual or recurrent neck disease. The chance of recurrent neck disease in patients with a CR and those with an ICR was 9% and 63%, respectively (P < .001). Also, those without recurrent neck disease after treatment were younger than those with neck disease (median age, 53 vs 64 years; P = .01) and had a higher initial Karnofsky Performance status score (P = .048).

The following factors did not seem to predict recurrent neck disease: sex, T category, N category (N2a and N2b vs N2c and N3), primary site (oropharynx vs other), initial hemoglobin level, cycles of cisplatin chemotherapy received, largest nodal diameter, and whether ND was performed. Of the 5 patients with N3 neck disease analyzed, 3 had locoregional control and 2 had residual disease and were not salvageable with surgery.

PATTERNS OF RECURRENTNESS

The actuarial 2-year locoregional recurrence-free survival for the entire cohort was 83%. Those who obtained a CR had a significant improvement in 2-year locoregional recurrence-free survival compared with those who did not obtain a CR (95% vs 25%) (Figure 4). At
Neck dissection has traditionally played an important role in the treatment of patients with SCCHN with regionally advanced disease (N2-N3). Since the 1970s, planned ND combined with radiotherapy has been considered standard treatment. However, as more effective chemoradiation regimens are used, the following question arises: Is routine planned ND still necessary for all patients with N2-N3 neck SCCHN after chemoradiation if a CR is achieved?

The goals of combined modality therapy are 2-fold: to increase cure rates and to preserve organ function.11 Of the 43 patients with N2 neck disease who achieved a CR (3 patients with N3 neck disease also had a CR), only 3 subsequently experienced a locoregional relapse during median follow-up of 35 months. Therefore, one could argue that most patients who respond well to treatment would not receive any further benefit from having a planned ND. Comparison of this study with the literature suggests that the present survival rates are comparable with those of other series that included planned ND after CR (Table 2). For example, according to Brizel et al,3 those who had a CR and a planned ND had overall and disease-free survival of 77% and 75%, respectively, at 4 years. In the present cohort, patients with a CR and no ND had 2-year overall survival of 81.7%. Other authors6,7,12,13,15 concur with these findings that patients undergoing planned ND after chemoradiation did not positively influence overall or disease-specific survival. However, other researchers14,16 would contend that planned ND is still necessary for advanced neck disease.

Several authors have concluded that conventional clinical and radiographic evaluation may not be an accurate predictor of pathologic response (overall accuracy, 54%-60%).5-11 In contrast, the present data show that a complete clinical or radiographic response was predictive of long-term locoregional control. Of the 46 patients with a CR and no planned ND, 2-year overall survival of 92% was achieved. The NPV was 93%. Three patients experienced a recurrence despite achieving a CR, and in only 1 of these patients was salvage surgery successful. These recurrences occurred as late as 24 months after treatment. A recent review of 550 patients with SCCHN treated at the University of Florida, Gainesville, has shown that a complete radiographic response on posttreatment CT had an NPV of 94%.17

Much of the literature, including the study by Lavertu et al,16 is in agreement that there is a need to find prognostic indicators of tumor response. Of several factors analyzed, CR, Karnofsky Performance Status score, and age showed some predictive value in this cohort. Younger patients (median age, 54 years) tended to have absence of neck disease after chemoradiation. This has not previously been reported in the literature. It has also been suggested that biological variables such as tumor oxygenation may predict clinical outcome.18 This was not assessed in our patients.

Most patients with N2 neck disease achieving a clinical CR after chemoradiation did not experience neck recurrence despite the absence of a planned ND. No comments can be made about patients with N3 neck disease.

![Figure 4. Locoregional recurrence-free survival in patients achieving a complete response (CR) and patients who had an incomplete response (ICR).](image)

Table 2. Literature Summary of ND After Chemoradiation for SCCHN

<table>
<thead>
<tr>
<th>Source</th>
<th>ND Status</th>
<th>Overall Survival, %</th>
<th>Locoregional Control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argiris et al,12 2004</td>
<td>ND, n = 91</td>
<td>58 (5 y)</td>
<td>CR with ND, 98%</td>
<td>ND recommended for N2 disease with ICR and N3 disease</td>
</tr>
<tr>
<td></td>
<td>No ND, n = 39</td>
<td>41 (5 y)</td>
<td>CR, no ND, 92%</td>
<td></td>
</tr>
<tr>
<td>Grabenbauer et al,13 2003</td>
<td>CR with ND, n = 56</td>
<td>44 (5 y)</td>
<td>80% (5 y)</td>
<td>ND did not make a difference in patients with CR</td>
</tr>
<tr>
<td></td>
<td>CR, no ND, n = 41</td>
<td>42 (5 y)</td>
<td>85% (5 y)</td>
<td></td>
</tr>
<tr>
<td>McHarm et al,14 2003</td>
<td>CR with ND, n = 32</td>
<td>NA</td>
<td>31/32 (97%)</td>
<td>Clinical CR did not predict pathologic CR</td>
</tr>
<tr>
<td></td>
<td>CR, no ND, n = 33</td>
<td>NA</td>
<td>29/33 (88%)</td>
<td></td>
</tr>
<tr>
<td>Brizel et al,3 2004</td>
<td>CR with ND, n = 27</td>
<td>77 (4 y)</td>
<td>75% (4-y DFS)</td>
<td>ND recommended for all N2-N3 disease</td>
</tr>
<tr>
<td></td>
<td>CR, no ND, n = 16</td>
<td>50 (4 y)</td>
<td>53% (4-y DFS)</td>
<td></td>
</tr>
<tr>
<td>Present series, patients with a CR only</td>
<td>CR, no ND, n = 46</td>
<td>92 (2 y)</td>
<td>95% (2-y LRFS)</td>
<td>N2 disease and CR may not require ND</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; DFS, disease-free survival; ICR, incomplete response; LRFS, locoregional recurrence-free survival; NA, not available; ND, neck dissection; SCCHN, squamous cell carcinoma of the head and neck.
because there were only 5 patients in this category. A limitation of this retrospective study is that only 30% of the patients with a CR had imaging after treatment. However, there was sufficient follow-up in the remaining patients with CR to ensure that any recurrences would have been detected. In patients who experienced a neck recurrence, only a few could undergo salvage surgery. Perhaps if routine planned ND had been offered to all 46 patients achieving CR, fewer delayed neck recurrences would have occurred. However, approximately 12 patients would require additional treatment to benefit 1 patient, or a number-needed-to-treat ratio of 12:1.

Some medical centers advocate the use of posttreatment fludeoxyglucose F 18–PET in determining the presence or absence of residual disease.20,21 The technical and timing issues regarding the use of this modality in the assessment of treatment response in head and neck cancer have been comprehensively reviewed.22 Further prospective studies using this modality are required to assess its value in addition to clinical and conventional CT/magnetic resonance imaging assessment. This may improve selection criteria for ND in patients with N2-N3 neck disease after chemoradiation. This trial is currently ongoing in the Ontario Cancer Oncology Group in Canada.

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Author Contributions: Drs Lau and MacKinnon had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lau. Acquisition of data: Lau and MacKinnon. Analysis and interpretation of data: Lau, Phan, and Matthews. Drafting of the manuscript: Lau. Critical revision of the manuscript for important intellectual content: Lau, Phan, MacKinnon, and Matthews. Statistical analysis: Phan. Obtained funding: Lau. Administrative, technical, and material support: Lau, Phan, MacKinnon, and Matthews.

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REFERENCES